

## **Remarks/Argument**

### **Pending Claims**

Claims 74 – 79, 84 – 86, and 89 – 93 remain in this application. Claims 77, 87, 88, 89 and 92 have been canceled. Claims 80 – 83, 94 – 109 have been withdrawn without prejudice. And, new claims 110-113 have been added.

### **Examiner Interview**

At the request of applicants, an examiner interview was conducted on June 1, 2011. At that time a proposed set of amended claims were presented in a form that was substantially similar to the currently amended claims. When applicants pointed out that claim 74 had been amended to exclude a solvent from the self-microemulsifiable base composition, the examiner indicated that a new prior art search would be needed to determine if the amended claim was patentable. As to claim 84, applicants argued, among other things, that the claimed ranges of propofol to water-immiscible solvent and to ethanol were not anticipated by the Hong reference because it did not describe the claimed ranges with sufficient specificity. It was agreed that applicants would submit a chart that compared the claimed ranges to the ranges disclosed by Hong in order to facilitate the analysis.

### **Summary of Claim Amendments**

Claim 74 has been amended to provide that the base composition does not contain a co-solvent. Claim 84 has been amended to provide a grammatical change and claim 93 has been amended to correct the numerical reference to a prior claim. Claims 80 and 104 are presented in a modified form. And, new claims 111 – 113 are presented.

### **Claim Rejections: 35 USC § 102**

The Examiner has rejected claims 74-76 and 78-79 under 35 U.S.C. § 102(b) as being anticipated by Hong et al. (KR 1020010055736, hereinafter “Hong”). Applicants respectfully disagree.

## Hong

Hong discloses and claims a “propofol microemulsion injection for general anesthesia injection formed by dissolving propofol in oil, and adding Solutol® HS 15 ... as a nonionic surfactant, and a suitable co-solvent or co-surfactant, and then simply stirring or mixing the solution [in water to form the microemulsion]” (page 5, second paragraph; and page 15, claim 1 [claiming “propofol dissolved in oil”]).

In response to the examiner’s contention that the rejected claims are anticipated by Hong, applicants have amended claim 74 to provide that, in addition to not containing a surfactant other than the claimed nonionic surfactant having the claimed formula, the self-microemulsifiable anhydrous base composition does *not* contain a co-solvent. This amendment is supported by applicants’ detailed specification and examples in which the claimed invention as in amended claim 74 does not include a co-surfactant or a co-solvent (page 14, paragraph [0021]; and pages 26-28, paragraphs [0044], [0045], and [0046]). Applicants submit that in view of this amendment to claim 74, the examiner’s contention that Hong anticipates claims 74-76 and 78-79 cannot be sustained.

To the extent that the examiner may argue that it would have been obvious to exclude a solvent from the composition disclosed in Hong, the reference specifically states that “[w]hen the concentration of the co-solvent or co-surfactant is about 1 wt% or less, [a] microemulsion is not formed”. This statement constitutes an express “teaching away” of the self-microemulsifiable base composition for use in forming a microemulsion as in amended claim 74, because claimed invention does not include any nonionic surfactant other than a nonionic surfactant having the claimed structure, and does not include a co-solvent (See M.P.E.P. §2144.05 (III) [“a prima facie case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention”; and *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) [“A reference may be said to teach away when a person of ordinary skill in the art, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant”]). As a result, claim 74 is not obvious in view of Hong, because the reference expressly teaches that a composition that is intended to be used to form a microemulsion

containing propofol must contain a significant amount of co-solvent or co-surfactant. Applicants' invention proves that this teaching in Hong is not correct.

Applicants have also submitted new claims that should logically be considered with amended claim 74. As pointed out above, Hong discloses and claims that the propofol of its composition is dissolved in oil. Accordingly, in order to further distinguish Hong from the claimed invention, new dependent claim 110 provides that the propofol contained within the base composition of amended claim 74 is not dissolved in oil. In addition to the above cited portions of applicants' specification that disclose that the claimed invention as in amended claim 74 does not contain a co-surfactant or co-solvent, the specification also discloses that the claimed invention does not disclose an oil in the base composition (page 12, paragraph [0015]). Accordingly, applicants submit that new claim 110 is not anticipated by Hong.

New independent claim 111 is substantially identical to amended claim 74 with the exception that the co-solvents that are excluded from the base composition have concentrations that are equal to or greater than about two (2) parts of co-solvent to about one (1) part of the nonionic surfactant. This claim is also not anticipated by Hong, because with one exception, all of the examples set forth in Hong disclose a composition containing amounts of co-solvent that equal two (2) or more parts of solvent to one (1) part of Solutol® HS 15. The exception is set forth in Hong's Example 4, wherein the water-miscible solvent glycerin is included in the composition in amount of one (1) part glycerin to one and one half parts (1.5) Solutol® HS 15. But this Example still does not anticipate claim 111, because the claim also provides that the nonionic surfactant is included in the base composition in an amount of about eight (8) or more parts of surfactant to one (1) part propofol. By comparison, Example 4 in Hong discloses that the Solutol® HS 15 is included in the composition in an amount of only three (3) parts Solutol® HS 15 to one (1) part propofol, substantially less nonionic surfactant than the minimum amount required by claim 111.

Next, independent claim 112 is substantially similar to claim 74 with the differences being that the nonionic surfactant is specified to be Solutol® HS 15, which is a commercial version of *PEG-660 12-hydroxystearate* and to further provide that the

base composition does not include a co-solvent other than the naturally occurring contaminants present in Solutol® HS 15.

Lastly, claim 113 is substantially the same as claim 111 with the only difference being that the nonionic surfactant is specified to be Solutol® HS 15.

#### Claim Rejections: 35 USC § 103

Since applicants' contend that amended claim 74 is not obvious over Hong for the reason set forth above, they now address the examiner's argument that claims 84-86 and 89-93 are unpatentable over Hong in view of Pace. In this regard, although the examiner argued in the non-final office action dated December 17 2010 that claims 84-86 and 89-93 were obvious over Dennis in view of Pace, the remarks and arguments submitted by applicants in reply to the non-final office action are equally applicable to the examiner's contention in the present final office action that the claims are obvious over Hong in view of Pace. Accordingly, applicants incorporate herein by reference the remarks and arguments they presented in their reply dated December 17, 2010 to the non-final office action and submit the following additional remarks and arguments.

The examiner contends that it would have been obvious to one of ordinary skill in the art to derive the relative concentrations of nonionic surfactant, water-immiscible and ethanol to propofol in base composition of claim 84 based upon concentrations of similar elements disclosed in Hong. Initially, applicants point out that Hong does not disclose the composition as in claim 84, which contains liquid propofol, a nonionic surfactant having the claimed formula, a *water-immiscible* solvent, and ethanol. Rather, the solvents disclosed by the Examples in Hong are all *water-miscible* solvents (i.e. polyethylene glycol 300, propylene glycol, glycerin, and N-methylpyrrolidone), and Hong does not disclose the use of ethanol *and* a water-miscible solvent in its composition (i.e. Example 1 [propofol, Solutol® HS 15, and ethanol]). As a result, it must be undisputed that Hong does not anticipate claim 84.

Next, applicants address the examiner's additional contention that it would have been obvious in view of Hong to derive the relative concentrations of propofol, nonionic surfactant having the claimed formula, water-immiscible solvent, and ethanol as set forth in claim 84. Before addressing this contention, applicants point out that Hong

does not disclose or suggest that a water-immiscible solvent could or should be substituted for a water-miscible one, nor does the reference disclose or suggest that a water-miscible solvent and ethanol could be combined in its composition and still produce high concentrations of propofol in the composition as illustrated in Hong's Example 5. As a result, it cannot be reasonably concluded that claim 84 is obvious over Hong. However, even if it were obvious that the substitutions and combinations could be made, the disclosure in Hong does not anticipate the composition ranges in claim 84 nor are the claimed ranges obvious over Hong.

In order to facilitate a comparison of the amounts of propofol, nonionic surfactant, water-immiscible solvent and ethanol as set forth in applicants' claim 84 to the amounts of propofol, nonionic surfactant, water-miscible solvent, and ethanol as described in the Hong Specification and Examples, applicants present the following summary:

Claim 84

1 part propofol dissolved in:

not less than 3 parts nonionic surfactant  
**0.3 to 0.5** parts water-immiscible solvent  
**0.5 to 0.6** parts ethanol

Hong (Specification, page 7)

1 part propofol dissolved in:

0.01 to 200 parts nonionic surfactant  
0.05 to 500 parts co-solvent or co-surfactant

Hong (Specification Examples, pages 8-10):

Example 1:

1 part propofol dissolved in:

5 parts Solutol® HS 15  
**5 parts Ethanol**

Example 2:

1 part propofol dissolved in:

10 parts Solutol ® HS 15  
**20 parts Polyethylene glycol 300**

Example 3:

1 part propofol dissolved in:

2.5 parts Solutol® HS 15  
**5 parts Propylene glycol**

Example 4:

1 part propofol dissolved in:

3 parts Solutol® HS 15  
**2 parts Glycerin**

Example 5:

1 part propofol dissolved in:

2 parts Solutol® HS 15  
**3 parts N-methylpyrrolidone**

As set forth in the above summary, the concentration ranges of water-immiscible solvent and ethanol described in claim 84 are very narrow: between 0.3 and 0.5 parts solvent to 1 part propofol and between 0.5 and 0.6 parts ethanol to 1 part propofol. By contrast, although the range for the co-solvent and co-surfactant described on page 7 of Hong does overlap the claimed ranges, the Hong reference teaches ranges that are exceedingly broad: between 0.05 to 500 parts of co-solvent or co-surfactant to 1 part of propofol. Accordingly, Applicants' submit that the range disclosed in Hong, which is approximately 500 times broader than the claimed ranges, does not teach the claimed ranges with "sufficient specificity" to anticipate the claim (See, *Atofina v. Great Lakes Chemical Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) [holding that a temperature range of 100-500 degrees C did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory]). This conclusion is further supported by the Examples set forth in Hong, which demonstrate that the requisite specificity is totally lacking. In each instance, the amounts of water-miscible co-solvent and ethanol (shown in the above summary in bold) utilized in the Hong formulation greatly exceeds the ranges for the water-immiscible solvent and ethanol set forth in claim 84 (also shown in

bold). As a result, the Hong disclosure itself teaches that the Hong ranges do not anticipate the claimed ranges.

Further, to the extent that is unclear whether the Hong reference teaches the claimed ranges of water-immiscible solvent and ethanol to propofol, the examiner must provide reasons to support the contention that the claim is anticipated by or is obvious over the reference (See, M.P.E.P. § 2131.03 (II)). The examiner states, among other things, that Hong differs from claim 84 insofar as Hong does not disclose the particular endpoints recited in the claim (i.e. 1.0 part propofol to 0.3 - 0.5 parts of water-immiscible solvent), but argues that since the reference teaches a broad range that overlaps the claimed endpoints, a *prima facie* case of obviousness is established. In response, applicants again point out that there is no overlap between the claimed ranges of propofol to water-immiscible solvent as compared to the ranges set forth in Hong's Examples. The only overlap that potentially exists arises from Hong's broad disclosure (not supported in any of the Examples) that 1 part of propofol can be dissolved in 0.05 to 500 parts of co-solvent. Thus, applicants contend that the determinative issue is not whether the broad ranges in Hong overlap the much narrower claimed ranges, but whether Hong teaches that the narrower ranges could be used in the formation of a base composition that could be used to form microemulsions containing concentrations of propofol of about 5% to 10%. The only teachings found in the Hong reference that are related to this issue are set forth in Hong's Examples 4 and 5. Example 4 discloses a composition that purports to contain a propofol concentration of 5% and a water-miscible solvent (glycerin) concentration of 10%; and Example 5 purports to disclose a composition containing 10% propofol and 30% water-miscible solvent (N-methylpyrrolidone). Although both of these examples disclose relatively high concentrations of propofol that are similar to the propofol concentrations claimed by applicants (See claims 104 and 105), the examples also require substantially higher concentrations of water-miscible solvent than the amounts of water-immiscible solvent claimed by applicants (See summary above comparing the ranges of claim 84 to the ranges disclosed in Hong's Examples). In this regard, there is no specific disclosure or teaching in Hong that water-immiscible solvents could be substituted for the miscible solvents. And, even if Hong suggested that the substitution could be made, Hong does

not disclose or teach that the amount of solvent could be substantially reduced and still be able to use the composition to form microemulsions containing high concentrations of propofol. Accordingly, applicants submit that the amounts of water-immiscible solvent as set forth in claim 84 are not obvious over Hong.

Applicants respectfully request that all claim rejections be withdrawn, that all pending claims be allowed, and that all withdrawn claims be considered for allowance.

Respectfully submitted,

By:

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